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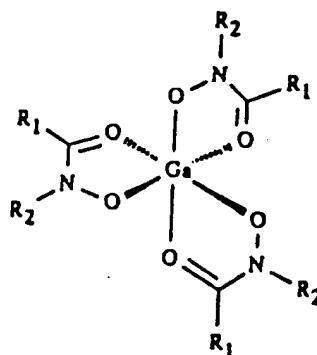
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(54) **Gallium compounds.**

(57) The present invention relates to compounds of gallium(III) which can be given orally to achieve high serum levels of gallium(III) for the treatment of hypercalcemia of malignancy and related disorders of bone metabolism.



EP 0 502 709 A1

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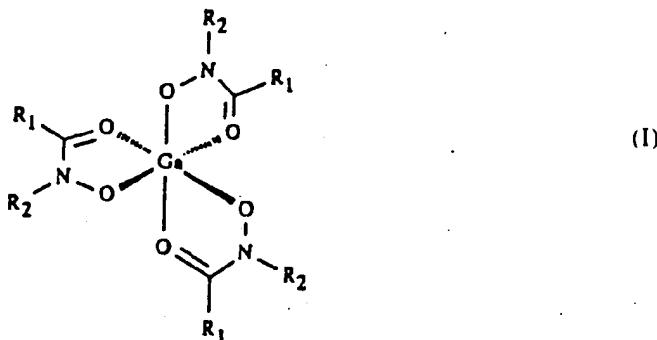
The present invention concerns gallium compounds which are well absorbed when administered orally.

Salts of the group 13 metal gallium have been known for some time to have antitumour activity. More recently, gallium has been shown to reduce serum calcium in patients with hypercalcemia of malignancy. Gallium exerts this latter effect by inhibiting the resorption of calcium from bone; it also increases bone strength so that gallium would also be useful for treating bone disorders associated with accelerated bone loss and decreased bone strength, (see eg. USP 4,704,277 and USP 4,529,593).

In practice, gallium therapy for hypercalcemia has been difficult to provide. It has been reported that renal toxicity is dose-limiting when gallium is administered as an iv bolus. A seven day continuous iv infusion of gallium showed no renal toxicity for the treatment of cancer-associated hypercalcemia, and while this therapy is effective, it is cumbersome. In order to make gallium therapy more conveniently administered for both cancer chemotherapy and the hypercalcemia of malignancy, and in order to provide wider application of gallium therapy to appropriate bone diseases, an oral dose form of gallium is highly desirable.

Drug absorption from the gastro-intestinal tract occurs at pH 4.5-7. In this pH range the gallium(III) aquo-ion is extensively hydrolysed to insoluble hydroxides and is very poorly absorbed. Daily oral doses of 400mg CaCl₃ in lung cancer patients yielded mean serum gallium concentrations of 371 ± 142 ug/mL. However, gallium in an appropriate co-ordination environment is stable to hydrolysis in aqueous environment, at pH which is relevant biologically.

The present invention provides novel hydroxamic acid complexes of gallium(III) which produce high serum levels of gallium when given orally compared to gallium salts. These complexes may be represented structurally by Formula I as follows:



35 where R₁ is C₁-C₈ n-alkyl and R₂ is H or C₁-C₂ alkyl, or R₁ and R₂ together form tetra- or penta- methylene.

(No stereochemistry is implied by this drawing)

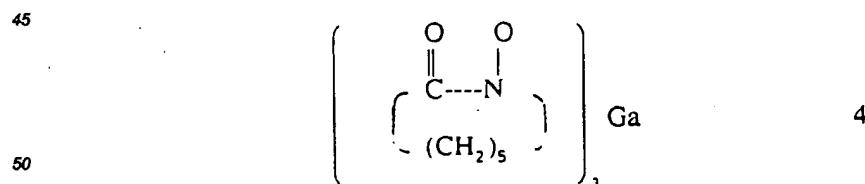
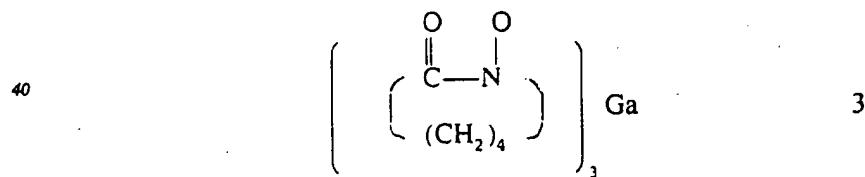
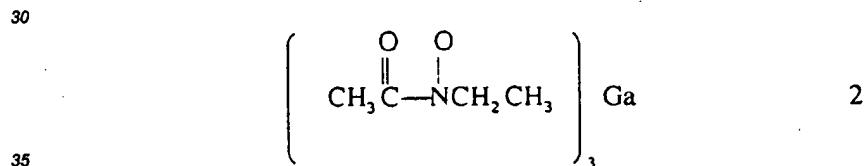
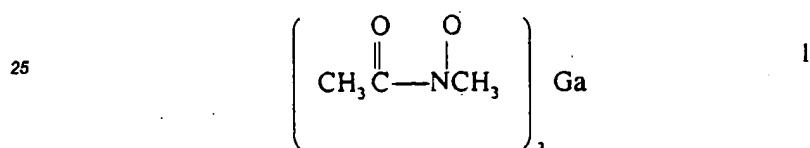
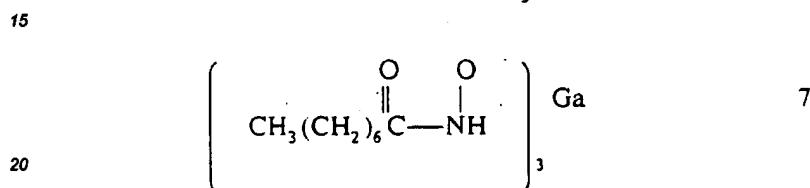
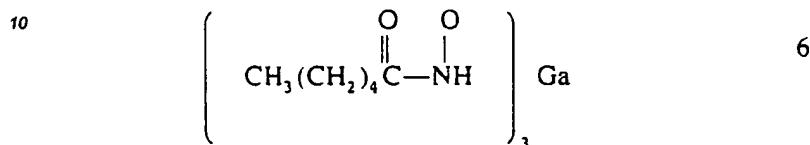
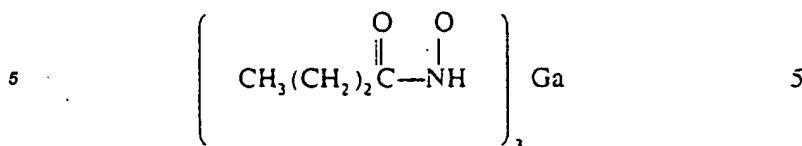
40 These complexes have not previously been prepared in pharmaceutically acceptable form. The compound of formula I where R is C₈ n-alkyl and R₂ is CH₃ has been disclosed in US Patent No 4,741,887 as an extract in the extraction of gallium from aqueous solutions also containing aluminium, iron and zinc.

45 As representative of the compounds of the invention the following may be mentioned:

50

55

Preparative Example No.



The complexes of the invention and the necessary starting materials may be prepared by procedures analogous to those generally known in the art and illustrated hereinafter. The gallium-containing starting materials are simple salts of gallium such as $\text{Ga}(\text{NO}_3)_3$ or GaCl_3 , or suspensions of freshly precipitated $\text{Ga(OH}_3\text{)}$. The hydroxamic acids are commercially available or may be prepared by reaction of an appropriate hydroxylamine with a carboxylic acid-ester or chloride to yield the free hydroxamic acid or its salt. (See B Monzyk et al, J Org Chem, 45, 4680 (1980) and Org Syn Coll Voll II. (1943) John Wiley & Sons, NY, p 67).

As noted, the complexes of the invention provide good oral absorption of gallium compared to commercially-available preparations used to treat cancer-related hypercalcemia. When assessed by *in vivo* tests in rats, as described hereinafter. The compounds are indicated for increasing the calcium content of bone tissue and for decreasing bone resorption, when administered in an effective amount.

5 The active complexes according to the present inventions may be administered in the form of pharmaceutical compositions formulated according to well known principles. Thus, the composition comprises the active ingredient, preferably in a unit dose, in admixture with a pharmaceutically acceptable diluent or carrier. The active complexes of the invention are accessed to have particular activity when taken orally, and therefore, preferred compositions are those formulated in the form of capsules, tablets, dragees or other solid compositions, 10 or as a solution or suspension, for example as a syrup, for oral administration. Suitable diluents and carriers and other components, and methods for formulation, are generally known.

10 Although the active complexes of the invention have particular utility for oral administration, the invention is not to be regarded as limited to methods of treatment and compositions solely for oral administration.

15 Thus, compositions for injections, suppositories, sustained release forms of such or for implantation and the like, may be formulated in conventional manner, and may provide advantages for particular courses of treatment or for combined therapy.

16 The present invention further provides a method of treatment for excessive loss of calcium from bone in a patient requiring such treatment and the other utilities mentioned herein, comprising administering to the patient an effective dose of an active complex of formula I. Preferably, the administration route is oral.

20 Dosage rates may suitably lie in the range of 0.1 to 100 mg/kg body weight. Preferably, the dosage is sufficient to maintain a level of 1 to 1.5 μ g gallium per ml of blood, and the dose may suitably be in the range 0.5 to 1.5g of gallium compound per day. Such a dose may be administered as a single unit dose or in a number of smaller unit doses. Other active compounds may be administered separately or together with the gallium complex, or supplemental therapy may be included in a course of treatment for a patient.

25

Example 1

Synthesis of (CH₃)CON(OH)CH₃

30 To 5.27g CH₃NHOH·HCl in 35ml MeOH at 0°C was added with stirring 22ml Et₃N dropwise. After stirring the suspension for 0.5 hr, 5.78g CH₃COCl was added dropwise over 5-10 min with vigorous stirring. After allowing the suspension to warm to room temperature, the precipitated Et₃N-HCl was removed by filtration and washed with ether. The ether washings were combined with the filtrate which was then stripped to dryness on a "rotovap" and stirred with 150ml Et₂O for 10 min. The suspension was filtered and the filtrate stripped to leave 35 4.3g yellow oil. The yellow oil was distilled, collecting everything below 90°C at 50 μ m Hg.

Synthesis of [CH₃CON(O)CH₃]₃Ga

40 A chloride-free suspension of freshly precipitated Ga(OH)₃ from 20ml 1.1m aqueous GaCl₃ in 120ml deionised water was stirred with 3.6g CH₃CON(OH)CH₃ for 16 hours. The suspension was centrifuged 10,000 rpm x 30 minutes and the supernatant stripped to dryness on the rotovap. The residue was stirred with hot absolute ethanol and the suspension centrifuged 15,000 rpm x 40 minutes. The supernatant was decanted and the volume reduced on the rotovap.

45 Addition of ether completed precipitation. The solid was filtered, washed with acetone and dried.

Analysis for C₉H₁₈GaN₃O₆ · ½H₂O

	% C	% H	% N	% Ga
50 Calc:	31.52	5.58	12.25	20.33
Found:	31.55	5.55	12.21	19.85

55

Example 2**Synthesis of CH₃CON(OH)CH₂CH₃**

5 A mixture of 5g N-ethylhydroxylamine HCl and 5.4g Na₂CO₃ was stirred at 0°C for 1 hours. 4.02g acetylchloride was added dropwise with stirring maintaining the temperature at 0°C. The suspension was filtered and the filtrate stripped of solvent to leave an oil which was distilled at 1mm Hg 85°C.

Synthesis of [CH₃CON(O)CH₂CH₃]₃Ga

10 To an aqueous suspension of chloride-free Ga(OH)₃ in 40ml H₂O prepared from 1.6g Ga(NO₃)₃.9H₂O was added 1.18g CH₃CON(OH)CH₂CH₃. The suspension was stirred overnight, filtered and stripped of solvent to leave an oil. The oil was dissolved in acetone and ether added to precipitate a white solid which was filtered, washed and dried.

15

Analysis for C₁₂H₂₄N₃O₆Ga·½H₂O

	<u>% C</u>	<u>% H</u>	<u>% N</u>
20	Calc:	37.43	6.54
	Found:	37.48	6.46
			11.14

Example 3**Synthesis of Br(CH₂)₄C(O)NH(OCH₂C₆H₅)**

30 A suspension of 18.75g of NH₂OCH₂(C₆H₅).HCl in 200ml CH₂Cl₂ was cooled to 0°C in an ice-NaCl bath. 30.35ml of triethylamine were added. A solution of 5-bromovaleryl chloride in 70ml CH₂Cl₂ was added dropwise while keeping the temperature of the cold suspension between 0-5°C. The suspension was stirred cold for 20 minutes, then removed from the bath and stirred at room temperature for 3 hours. The reaction mixture was washed with 3 x 100ml 1N HCl, 3 x 100ml sat. NaHCO₃ and 3 x 100ml sat. NaCl solution. The organic layer was dried over MgSO₄, filtered and solvent removed to yield 27.38g of green-grey oil.

35

Synthesis of CH₂CH₂C(O)N(OH)CH₂CH₂

40 To 5g of Br(CH₂)₄C(O)NH(OCH₂C₆H₅) was added 19.2ml of 1 M NaOH. The two-phase system was stirred for 30 minutes then extracted with 3 x 25ml CH₂Cl₂. The organic layers were combined and dried over MgSO₄, filtered and solvent removed leaving 3.23g of white solid. This solid was mixed with 70ml of 95% EtOH and 0.323g of 10% Pd on carbon. The mixture was hydrogenated for 1 hour at 50 psi (3.45 bar). The reaction mixture was filtered through diatomaceous earth and the solvent removed leaving 1.70g of yellowish greasy solid.

45

Synthesis of [CH₂CH₂C(O)N(O)CH₂CH₂]₃Ga

50 To a suspension of freshly precipitated Ga(OH)₃ from 5.9ml of 1.1 M GaCl₃ in 40ml H₂O was added a clear solution of 1.5g CH₂CH₂CON(OH)CH₂CH₂ in 60ml H₂O and stirred for 72 hours at room temperature. The solvent volume was reduced by 25% on the rotovap and centrifuged at 15.000 rpm for 40 minutes. The H₂O from the clear supernate was evaporated leaving a gummy residue. The residue was dissolved in 50.ml H₂O, filtered through celite and the solvent removed. The remaining yellow lacquer was recrystallised from Abs ethanol/ether to yield 100mg of orange solid.

Analysis for $C_{15}H_{24}N_3O_6Ga \cdot \frac{1}{2}H_2O$

5	<u>% C</u>	<u>% H</u>	<u>% N</u>	<u>Ga</u>
	Calc: 42.78	5.98	9.98	16.56
	Found: 42.83	5.98	9.75	16.69

10 Example 4

Synthesis of $BrCH_2(CH_2)_4C(O)NH(OCH_2C_6H_5)$

15 To 4.43g of $NH_2OCH_2(C_6H_5)\cdot HCl$ in 50 ml of CH_2Cl_2 at 0°C in an ice-NaCl bath was added 7.17ml of triethylamine. The temperature was kept between 0-5°C while a solution of 3.58ml 6-bromothexanoyl chloride in 15ml CH_2Cl_2 was added dropwise. The mixture was stirred cold for 20 minutes then the ice bath was removed, it was stirred for another 3 hours at room temperature. The mixture was extracted with 3 x 25ml 1N HCl solution and 3 x 25ml sat. NaCl solution. The organic layer was dried over $MgSO_4$, filtered and stripped of solvent, leaving 6.56g of oil that solidified after being left open to the air.

20

25 Synthesis of $CH_2CH_2C(O)N(OH)CH_2CH_2CH_2CH_2$

A solution of 18.7ml of 1 M NaOH and 5.1g of $BrCH_2(CH_2)_4CH_2NHOCH_2-C_6H_5$ were mixed together and heated to 80°C. After 10 minutes, a white precipitate came out of the slightly turbid solution. It was stirred at 80°C for another 10 minutes. The mixture was extracted with 3 x 20ml CH_2Cl_2 . The organic layers were dried over $MgSO_4$, filtered and solvent removed, leaving 3.42g of yellow oil. The oil was dissolved in 50ml MeOH, 0.342g of 10% Pd/C was added and the mixture reduced in a Parr reactor under 50 psi (3.45bar) H_2 for 2 hours. The reaction mixture was filtered through diatomaceous earth, and stripped of solvent leaving 1.91g of yellow oil which solidified after being exposed to air. The solid was sublimed in a Kugle Rohr apparatus at 50µm Hg, 60°C to yield 1.15g.

35

Synthesis of $(CH_2(CH_2)_3C(O)N(O)CH_2)_3Ga$

40 A chloride-free suspension of freshly precipitated $Ga(OH)_3$ from 1.8ml 1.1 M aqueous $GaCl_3$ in 20ml H_2O was stirred a filtered solution of 0.5g $CH_2(CH_2)_3C(O)N(OH)CH_2$ in 20ml of H_2O . The suspension was stirred for 3 hours, then heated to 50°C for 1.5 hours, and finally stirred at room temperature for 15 hours. The cloudy solution was centrifuged at 15.000 rpm for 15 minutes and supernate was stripped of H_2O . 450mg of white solid was collected.

45

Analysis for $C_{18}H_{30}N_3O_6Ga$

50	<u>% C</u>	<u>% H</u>	<u>% N</u>	<u>Ga</u>
	Calc: 47.60	6.66	9.25	15.35
	Found: 47.36	6.68	9.13	14.62

55 Example 5

Synthesis of $[CH_3(CH_2)_2CON(O)H]_3Ga$

To free hydroxylamine in methanol generated from 20g hydroxylamine hydrochloride and 24.11g KOH as

in Example 6 below was added, 16.47g ethyl butyrate. The solid KCl which formed was filtered off and washed with methanol. After several hours, more precipitated KCl was filtered off, and the filtrate evaporated of solvent to leave a damp crystalline solid. The solid was recrystallised from hot 8:1 acetone/ethanol, washed with ethyl acetate and dried to yield 8.9g $\text{CH}_3(\text{CH}_2)_2\text{CON}(\text{OK})\text{H}$.

5 To 2g $\text{CH}_3(\text{CH}_2)_2\text{CON}(\text{OK})\text{H}$ in 50ml methanol was added 1.97g $\text{Ga}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ in 50ml methanol. Solid KNO_3 was removed by filtration and the filtrate evaporated of solvent. The residue was triturated with 10:1 methylene chloride/methanol to precipitate KNO_3 which was removed by filtration. The filtrate was evaporated of solvent to leave a pink oil. The pink oil was stirred in ethyl acetate to yield 1.34g of white solid.

10 Analysis for $\text{C}_{12}\text{H}_{24}\text{N}_3\text{O}_6\text{Ga}$

	<u>% C</u>	<u>% H</u>	<u>% N</u>	<u>% Ga</u>
15 Calc:	38.33	6.43	11.17	18.54
Found:	38.08	6.145	11.07	18.01

20 Example 6

Synthesis of $(\text{CH}_3(\text{CH}_2)_4\text{CON}(\text{O})\text{H})_3\text{Ga}$

25 Two mixtures of 8.4g hydroxylamine hydrochloride in 60ml methanol and 10.2g KOH in 30ml methanol were heated to boiling to make complete solutions. To the cooled (40°C) solution of hydroxylamine hydrochloride, under a N_2 flush, was added with stirring the hot methanolic solution of KOH during which a precipitate of KCl formed. After cooling, the mixture was stirred for 5 minutes, and the white solid filtered off. Additional KCl formed in the filtrate and was removed by filtration. The volume of the filtrate was reduced to 100ml by evaporation and kept at -20°C for 16 hours. The white gummy crystalline solid which formed was recrystallised from 100ml hot absolute ethanol. A total of 3 crops yielded 3.7g $\text{CH}_3(\text{CH}_2)_4\text{CON}(\text{OK})\text{H}$.

30 To 0.9ml 1.1 M aqueous GaCl_3 in 80ml water at 80°C was added with stirring 0.5g $(\text{CH}_3)(\text{CH}_2)_4\text{CON}(\text{OK})\text{H}$ in 10ml water. The volume of the solution was reduced to 50ml by evaporation, and a sticky substance formed. The mixture was allowed to stand at room temperature for 16 hours. 40ml 50/50 methanol/water was added to the mixture which was heated to form a complete solution. 0.25g white solid was collected after 3 days.

35

Analysis for $\text{C}_{18}\text{H}_{36}\text{N}_3\text{O}_6\text{Ga} \cdot \text{H}_2\text{O}$

	<u>% C</u>	<u>% H</u>	<u>% N</u>	<u>% Ga</u>
40 Calc:	45.21	8.01	8.79	14.58
Found:	45.34	7.79	8.75	14.30

45 Example 7

Synthesis of $(\text{CH}_3)(\text{CH}_2)_6\text{CON}(\text{O})\text{H})_3\text{Ga}$

50 To a stirred suspension of 1g of $\text{CH}_3(\text{CH}_2)_6\text{CON}(\text{OK})\text{H}$ in 120ml water was added 2ml 1.1 M aqueous GaCl_3 . After about 3 hours the pH was adjusted to 6. A white solid was filtered, washed with water and dried. The white solid was recrystallised by careful addition of water to a methanolic solution of the white solid to yield 550mg white solid.

55

Analysis for $C_{24}H_{48}N_3O_6Ga \cdot H_2O$

	<u>% C</u>	<u>% H</u>	<u>% N</u>
5	Calc:	51.26	8.96
	Found:	51.37	8.83

10 According to the invention, compounds were tested for oral absorption in rats. Male Sprague Dawley rats weighings 150-225g were purchased from Harlan Sprague Dawley Inc (Indianapolis, IN). The gallium standard solution is from Aldrich Chemical Co (Milwaukee, WI). Metofane is a product from Pitman-Moore (Mundelein, IL), and all other chemicals are commercially available. Gallium test compounds were dissolved in 18 megohm water (Millipore, Bedford, MA) or suspended in 0.5% carboxymethyl cellulose in 5% ethanol, if the compound
15 was not water soluble. The suspension were sonicated at room temperature for about 5 minutes.

For stomach and intestine administrations, rats were anaesthetised with metofane, and a one-inch incision made to expose the stomach and a portion of the small intestine. A ligation was made immediately below the pylorus, and a second ligation was made one-cm below to assure no leakage. For oral gavage administration, 18-gauge ball-tipped animal feeding needles (Popper & Sons, Inc, New Hyde Park, NJ) were used. For stomach injections, needles were inserted in the middle of the pyloric part of the stomach which has an opaque thick muscular wall, and intestinal injections were made about 0.5cm below the second ligation with the needle pointed down and away from the stomach.

Sutures were made with 3-4 stitches with 3-0 silk surgical thread (Ethicon Inc, Somerville, NJ). The tail vein was used for intravenous injections. With the exception of oral gavage administrations, all injections were made with 30-gauge needles to minimise the possibility of leakage. The dose was 0.067mmol/kg. Approximately 300 μ l blood samples were collected at 0.17, 0.5, 1.0, 2.0, 4.0 hours following compound administration. The blood was placed in 1ml Eppendorf tubes precoated with 50 μ l heparin (1,000 U/ml and air dried, so there was no blood dilution involved. The plasma was recovered after the blood was centrifuged for 2 minutes in a Fischer Micro-centrifuge. Model 235B, and its gallium content measured by a Varian Flameless Atomic Absorption Spectrometer. The standard curve was linear in the gallium concentrations of 5-100ng/ml. The area under the concentration versus time curve (AUC) for 0-4 hours was estimated.

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Four-Hour Under Curve0.067mmol/kg

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	<u>Compound</u>	<u>Example No.</u>	<u>4h-AUC</u>
			(ng//ml)h
10			
15	$\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{N} \\ \\ (\text{CH}_2)_4 \end{array} \right)_3 \text{Ga}$	3	4469
20	$\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{C}-\text{NCH}_3 \end{array} \right)_3 \text{Ga}$	1	2966
25	$\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3(\text{CH}_2)_4\text{C}-\text{NH} \end{array} \right)_3 \text{Ga}$	6	2214
30	$\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3(\text{CH}_2)_2\text{C}-\text{NH} \end{array} \right)_3 \text{Ga}$	5	1592
35	Ga(NO ₃) ₃	(Comparison)	897

40

A solution of gallium nitrate in citrate buffer is given as a control to show the intestinal absorption of a commercial preparation.

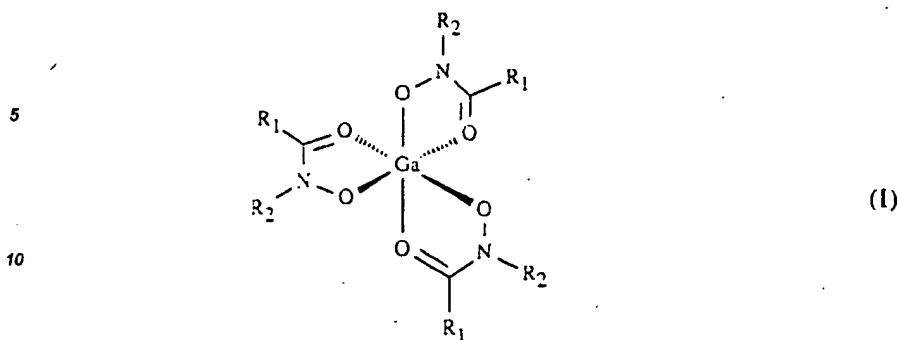
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The 4-hours AUC's indicate that good oral absorption of gallium occurs from the intestine and that appropriate formulation of the gallium compounds will yield a convenient dose form of gallium for the treatment of cancer, the hypercalcemia of malignancy and other diseases characterised by excessive bone loss and bone weakening.

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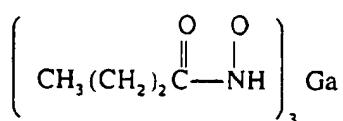
1. A pharmaceutical composition for administering gallium to a patient, comprising a gallium(III) complex of formula I

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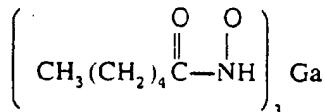


where R_1 is C_1-C_8 n-alkyl and R_2 is H or C_1-C_2 alkyl, or R_1 and R_2 together form tetra- or penta- methylene, in pharmaceutically acceptable carrier or diluent.

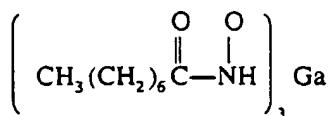
20 2. The composition of claim 1, wherein the complex is



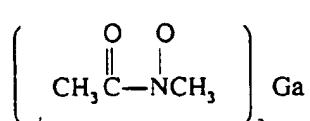
30 3. The composition of claim 1, wherein the complex is



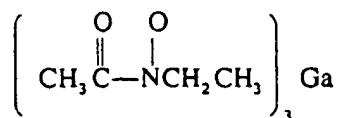
40 4. The composition of claim 1, wherein the complex is



50 5. The composition of claim 1, wherein the complex is



6. The composition of claim 1, wherein the complex is



7. The composition of claim 1, wherein the complex is



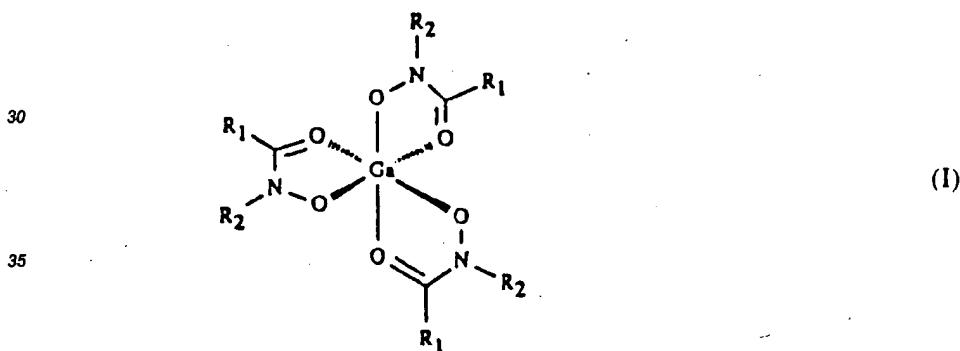
10 8. The composition of claim 1, wherein the complex is



20 9. The composition of claim 1, in a form for oral administration.

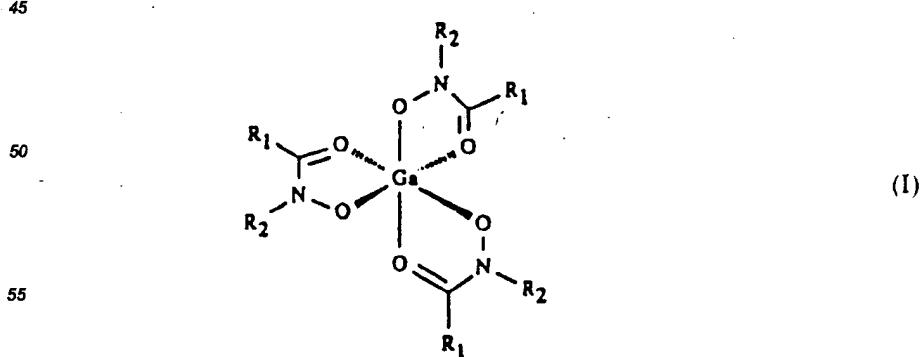
10. The composition of any one of the preceding claims, in unit dosage form.

25 11. A gallium(III) complex of formula I,



40 where R₁ is C₁-C₈ n-alkyl and R₂ is H or C₁-C₂ alkyl, or R₁ and R₂ together form tetra- or penta- methylene, in pharmaceutically acceptable form.

45 12. A gallium(III) complex of formula I,



where R₁ is C₁-C₈ n-alkyl and R₂ is H or C₁-C₂ alkyl, or R₁ and R₂ together from tetra- or penta- methylene,
provided that when R₁ is C₈ n-alkyl then R₂ is not CH₃.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 1851

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)												
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim													
A, D	US-A-4 529 593 (R. P. WARRELL ET AL.) * claims * ---	1-12	C07C259/06 C07D211/94 C07D211/10												
A	EP-A-0 325 559 (CIBA-GEIGY A. G.) * claims * ---	1-12													
A	EP-A-0 271 468 (MONSANTO COMPANY) * claims * ---	1													
A	JOURNAL OF ORGANOMETALLIC CHEMISTRY. vol. 99, no. 2, 14 October 1975, LAUSANNE CH pages 223 - 230; H.-U. SCHEWERING ET AL: 'DIALKYLMETALLHYDROXAMATE-MONOMERE METALLORGANISCHE FUNFRINGMOLEKULE DES GALLIUM, INDIUMS UND THALLIUMS' * page 225 - page 226 *	1													
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)												
			C07C C07F C07D												
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>15 JUNE 1992</td> <td>SANCHEZ GARCIA J.M.</td> </tr> <tr> <td colspan="3"> CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document </td> </tr> <tr> <td colspan="3"> T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document </td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	15 JUNE 1992	SANCHEZ GARCIA J.M.	CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document		
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